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Long-Term Stimulation of a Diaphragm Muscle Pouch[1]

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The availability of the diaphragm muscle makes it a logical potential source of power for myocardial assistance. As early as 1959 Kantrowitz and McKinnon [1] reported the effects of electrically stimulating diaphragm muscle wrapped around the ventricles or around the descending thoracic aorta in the dog; stimulation of the ventricular graft during systole did not raise mean aortic pressure, but stimulation in diastole of the aortic graft momentarily raised the aortic pressure and augmented coronary blood flow. No experiment was longer than 1 min.

In 1964, in one experimental animal, Nakamura and Glenn [5] were able to demonstrate an increase in systolic pressure when a wraparound graft to the ventricles was stimulated for several minutes.

Shepherd [7] applied denervated pedicled diaphragm grafts to the right ventricle. After several months those muscle grafts continuously paced with an implanted pacemaker remained viable without loss in mass while those that were not paced atrophied after several weeks. Contractility was observed in a majority of the chronically paced grafts upon external stimulation, though no measurements of the contractile forces generated within the grafts were made. Furthermore, there was no augmentation of cardiac output upon external stimulation of the diaphragm applied to the right ventricle.

Kunov *et al.* [2] studied the mechanical properties of the diaphragm in the dog, utilizing a hydraulic pouch method of their own design. A wide range of pressure responses of the muscle was noted when voltage, frequency, pulse duration, and baseline pressures within the pouch were varied. The studies suggested that the stimulated diaphragm could generate pressures equal to those in the right ventricle for periods of at least 4 hr.

Kusaba and co-workers [3] wrapped a pedicle diaphragm graft about the left ventricle after ligation of the left coronary artery; hemodynamic augmentation was achieved with synchronous stimulation during alternate systoles for up to 3 hr. However, if stimulation occurred during every systole, augmentation continued for less than 1 hr. These results were said to indicate that blood flow to the graft was impeded during its contraction.

These various experiments demonstrated that a portion of diaphragm muscle could survive as a pedicled graft, retain its contractility, and, for brief periods, generate pressures commensurate with those in the right side of the heart and pulmonary artery. We wished to determine whether such a graft, if rhythmically stimulated, was capable of the prolonged and consistent response necessary to make it useful for cardiac assistance.

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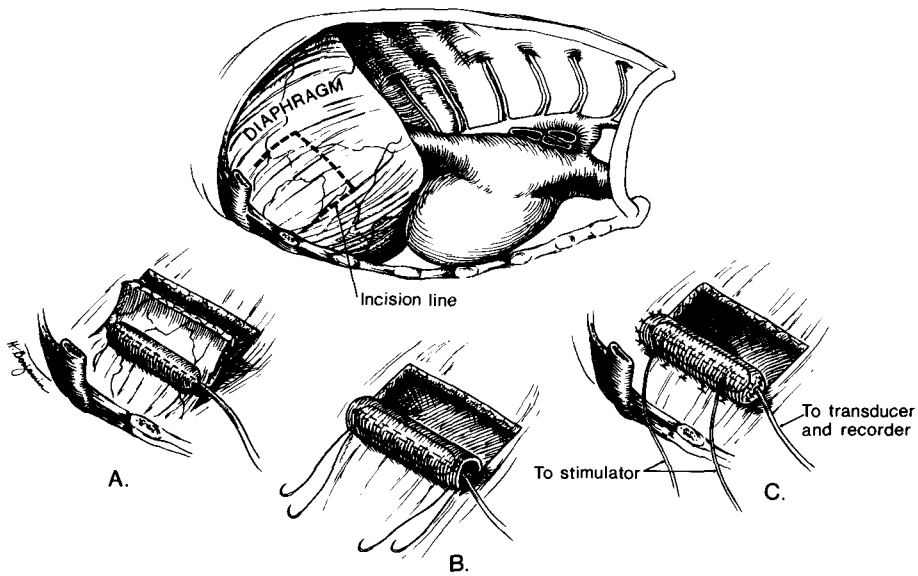

FIG. 1. The process of forming a cylindrical pouch from an incised segment of diaphragm. The flap is folded over a small balloon (A), the posterior edge is secured to that part of the diaphragm still in place with simple interrupted sutures (B), and electrodes are fastened to the pouch wall (C).

METHODS

Eight mongrel dogs weighing 26 to 34 kg were used. Anesthesia was induced with iv thiamylal sodium,[3] 0.5 mg/kg, and after intubation was maintained with methoxyflurane.[4] Each animal was ventilated with a volume- and pressure-controlled respirator.[5] After thoractomy through either the seventh or eighth right intercostal space, the chest was retracted widely. A portion of retrosternal diaphragm (Fig. 1) not incorporating the central tendon was mobilized by incising it on three sides, preserving the anterior attachment to the chest wall with the musculophrenic vessels; the sternal branch of the right phrenic nerve was transected [4] to preclude stimulation of the remaining hemidiaphragm by antidromic transmission of impulses as described by Randic and Straughan [6]. The posterior edge of the 8 × 6-cm flap was folded forward upon the fixed anterior portion and sutured there with simple, interrupted sutures to reduce obstruction of blood flow. A flaccid condom balloon was inserted into the cylindrical pouch thus created [2]. No attempt was made to close the defect in the hemidiaphragm. Two stainless-steel braided-wire electrodes were sewn into the wall of the pouch, and the balloon was filled with normal saline, giving a baseline pressure of 18 mm Hg. A stiff catheter led from the interior of the pouch to a pressure transducer connected in turn to a Brush recorder.[6] The condition of the pouch was observed for several minutes and any questionable or frankly cyanotic areas were excised with revision of the pouch. The chest wound was approximated with a Stille–Bailey rib clamp before an experiment was begun. The appearance of the pouch was noted periodically as long as the stimulation was continued. Blood pressure in the right carotid artery was recorded continuously by means of a fluid-filled catheter in line with a pressure transducer.[7]

[3] Surital (Parke–Davis).

[4] Metofane (Pitman–Moore) in a Metomatic Model 980 anesthesia machine (Pitman–Moore).

[5] Metomatic ventilator (Pitman–Moore).

[6] Gould Brush 480, Gould, Inc., Cleveland, Ohio.

[7] Statham P23Dd, Ser. No. 15563, Hato Rey, Puerto Rico.

TABLE 1

SUMMARY OF EXPERIMENTS

Experiment number	Voltage (V)	Duration of stimulation (hr)	Initial pressure increase (mm Hg)	Final pressure increase (mm Hg)	Reason for termination
1	3.6	3.5	78	33	Arrhythmia, arrest
2	3.6	18.5	35	2	Pouch infarction
3	3.6	1	42	43	Hypotension, arrhythmia, arrest
4	3.6	15.5	35	5	Hypotension, shock
5	7.0	14	38	16	Hypotension, arrhythmia
6	7.0	20	43	0	No pouch pressure
7	3.6	3.5	43	9	Arrythmia, arrest
8	7.0	4.5	40	13	Power unit failure

ECG was monitored continuously through standard limb leads.

Stimulation was provided with a pair of Grass stimulators[8] using protocols consistent with those of Kusaba *et al.* [3] and Kunov *et al.* [2]. The minimum voltage necessary to achieve initial pressures within the pouch comparable to pressures in the right ventricle was used. The desirable level was found to be either 3.6 or 7 V. Biphasic pulse trains were used with pulse widths (duration) of 0.5 msec, 8 pulses/train 5 msec apart, with an interval of 500 msec between trains. This pacing produced 120 contractions/min, which were not synchronized with the heart beat. Except in one instance when a power failure caused the experiment to be terminated, stimulation was applied continuously until either death of the dog or cessation of pressure generation in the pouch.

RESULTS

Five of the eight pouches were stimulated with 3.6 V but three required 7 V to achieve similar initial pressure increases. Except for one dog which developed severe hypotension and a lethal arrhythmia after 1 hr, duration of stimulation ranged from 3.5 to 20 hr with a mean of 10 hr. Pressures generated initially were 34–43 mm Hg above the baseline in seven dogs (Table 1); in one dog the initial pressure generation was inexplicably 78 mm Hg and could not be reproduced at reasonable voltages in subsequent dogs.

The changes in mean pouch pressures and mean blood pressures with time are shown in Fig. 2. Standard deviations are also indicated for the pouch pressures. In general, the data reveal that there was a rapid decrease in pouch pressures over the first 4 hr, averaging more than 55% of the initial pressures. Afterwards, although the decline was progressive, it was more gradual (Fig. 2, which excludes Experiment 3 of Table 1). No significant statistical correlation between mean blood pressure and the pouch pressure was found.

Experiments were terminated for several reasons (Table 1): Four dogs developed lethal arrhythmias. Of this group, one arrhythmia and arrest developed precipitously soon after initiation of stimulation, while two occurred after a brief period of ventricular arrhythmia following 3.5 hr of stimulation. After a progressive decrease in blood pressure, one animal developed lethal arrhythmia after 14 hr; another animal developed progressive hypotension after 10.5 hr and required an isoproterenol (Isuprel)

[8] Model S4D, Grass Instrument Co., Quincy, Massachusetts.

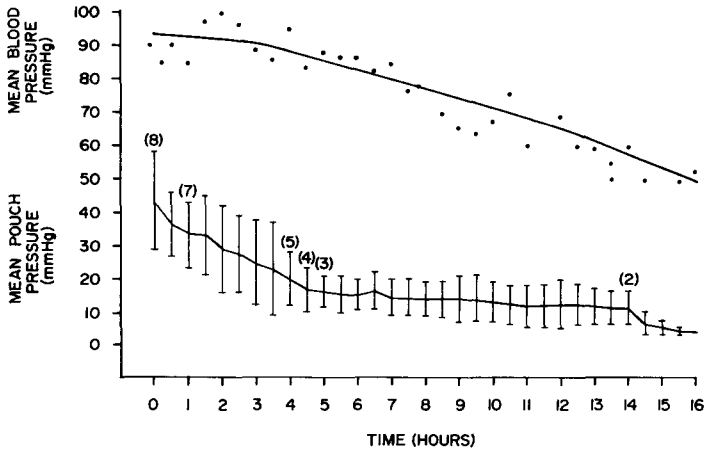

FIG. 2. The change in mean arterial pressure and mean pouch pressure with time. The numbers in parentheses represent the number of animals whose pouch pressures were measured at the time indicated.

drip to sustain blood pressure. Irreversible cardiogenic shock ensued after 15 hr. In one study the condition of the animal remained stable but the power unit failed.

Judged by their appearance and the pressures they generated, the pouches remained viable as long as the systolic blood pressure remained above approximately 60 mm Hg. Cyanosis and eventual infarction followed once the blood pressure fell below this level, irrespective of the duration of stimulation. Two studies had to be terminated after more than 18 hr even though the cardiovascular condition of the animals was stable. In one case the pouch developed a total infarct after 18.5 hr and in the other case the pouch appeared viable after 20 hr but had ceased to generate pressure. In a third case (Experiment 5) a portion of the pouch developed cyanosis after 12 hr of stimulation but infarction never occurred.

DISCUSSION

In all previous investigations of this nature, stimulation of the diaphragm was either of short duration to achieve temporary myocardial assistance or was applied for a prolonged period using a minimal voltage to prevent atrophy of the denervated graft. As shown by Kunov *et al.* [2], a diaphragm hydraulic pouch in the dog can achieve pressures of 176 mm Hg when 30 V is used. However, the muscle rapidly fatigues. In the experiments reported here we chose conditions which were consistent with those used by others but which their data suggested would not result in rapid muscle fatigue.

All diaphragm pouches displayed a rapid initial decline in pressures generated followed by a slower but still progressive fall. In five experiments (1, 3, 4, 5, and 7) the rates at which the pressures dropped may have been increased by hypotension and arrhythmia. Two instances of hypotension are thought to have been the result of surgical complications. In one case the death after 1 hr (Experiment 3) may have resulted from inadvertent obstruction by the pouch of venous return through the inferior vena cava. In the other case (Experiment 4) progressive hypotension leading to irreversible shock may have been secondary to slow hemorrhage from the chest wound. In the other three experiments the animals died without apparent cause following the paroxysmal onset of ventricular arrhythmias. In these instances it is possible that the primary reason for cardiovascular deterioration was electrical interference with myocardial conductivity by the power unit

stimulating the pouch. Though the antidromic transmission of impulses to the remaining hemidiaphragm was effectively precluded by the denervation of the pouch, no further provisions for electrical insulation had been made.

In the experiment terminated by a power failure (Experiment 8), a progressive decline in pouch pressure was observed in the presence of cardiovascular stability.

The outcome of two experiments is thought to be due neither to surgical complications nor to the electrical equipment. The conditions of the two animals remained stable after 18 hr of continuous stimulation; in neither did arrhythmias or fluctuations in blood pressure occur during the course of the experiment, yet pressures within the pouch were not sustained. In one dog (Experiment 2) the pouch developed an infarct after more than 18 hr of stimulation despite good systolic pressures, while in the other dog (Experiment 6) the pouch appeared viable but no pressures were generated within it. Again, failure was not clearly caused by muscle fatigue alone. If contractions of the pouch interfered with its own perfusion or if the pouch was twisted about its base, blood flow to the muscle may not have been sufficient to support contractile work. By pacing the diaphragm every other rather than each systole, Kusaba *et al.* [3] obtained longer periods of contraction which they attributed to less frequent impedance of blood flow during muscle contractions. Though in the experiments reported here stimulation was not synchronized with the heart cycle, over a prolonged period of time a percentage of pouch contractions would coincide with its period of perfusion thus hastening muscle fatigue. When coefficients of correlation between mean blood pressure and pouch pressure per unit of time were obtained, no significant relationship was found; moreover, no twisting of the pouch about its pedicle was observed. It appears, therefore, that in these last two cases the one other factor besides muscle fatigue contributing to a progressive decrease in pouch pressures may have been impedance to blood flow.

Lastly, diminution of pressures generated by the pouches could have been associated with increased electrical resistance from polarization or corrosion of the electrode surface in contact with the muscle or with the desiccation of adjacent tissue and the formation of a protein coagulum on the electrode, as postulated by Stemmer *et al.* [8]. An argument against this explanation is that the results observed did not appear to be related to the voltages used; chronic stimulation was achieved at both voltages with more frequent occurrence of hypotension and arrhythmias at the lower voltage. With one exception the initial pressures achieved were comparable. In the one case (Experiment 1) initial pressure was nearly twice as great as in other experiments with less rapid deterioration of pouch pressures once the initial decline had occurred. The reason for this high pressure is not apparent.

In summary, the progressive decline in diaphragm pouch pressures observed in these experiments cannot be attributed solely to fatigue of the muscle but appears to have been influenced by the cardiovascular condition of individual animals and perhaps by decreased perfusion of the pouch during its contractions, although only two pouches exhibited cyanosis or infarction and statistical analysis failed to reveal a significant correlation between carotid mean blood pressure and pouch pressure. The results do not support the hypothesis that the work of the heart can be sustained by such a graft for longer than a few hours. A continual decrease in the pressure generated in all pouches were evident. Further studies in which there was insulation of the heart from electrical interference and in which stimulation of the pouch was timed to occur during diastole could have been added. Nevertheless, it is our conclusion that stimulation of a graft constructed from the diaphragm for purposes of myocardial assistance is not feasible.

SUMMARY

Denervated hydraulic pouches were fashioned from a retrosternal portion of the right hemidiaphragm and electrically stimulated for several hours at voltages selected to achieve pressures commensurate with those encountered in the right ventricle. The data revealed a progressive decline in pressures generated by the pouch with time, the deterioration perhaps enhanced by impaired perfusion of the pouch but statistically independent of systemic blood pressures. Therefore it was concluded that contraction of the diaphragm muscle could not be used clinically to assist the heart.

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